NOVEL OLANZAPINE FORMS AND RELATED METHODS OF TREATMENT

FIELD OF THE INVENTION

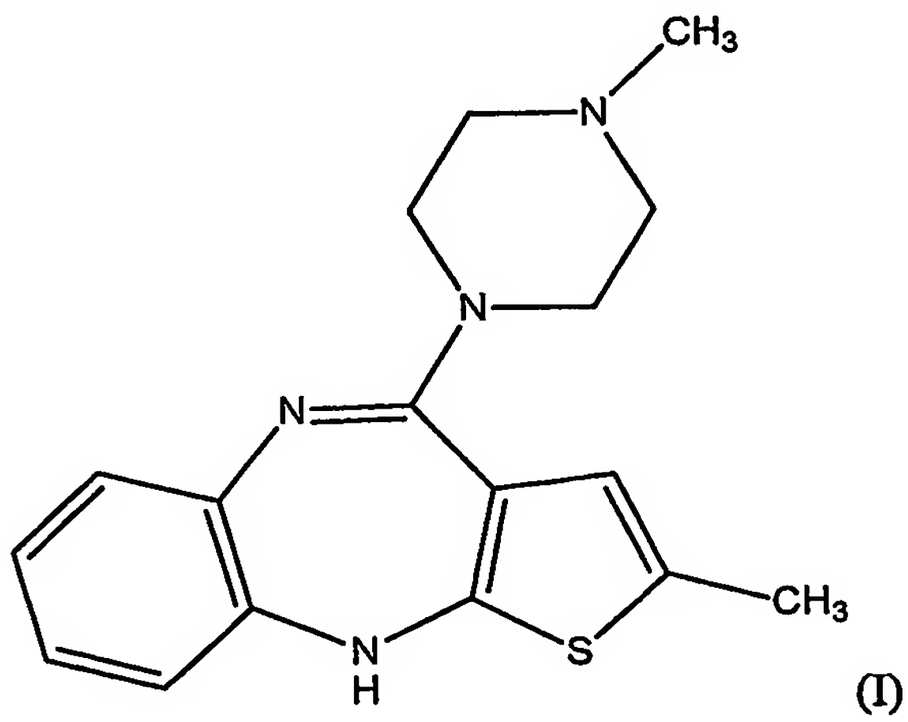
The invention provides novel soluble olanzapine forms. These forms include salts, co-crystals, and solvates of olanzapine.

The invention also provides novel pharmaceutical compositions comprising these novel soluble forms and related methods of treatment.

Compositions and methods of the invention of the invention are useful in the treatment of psychosis and functional bowel disorders.

BACKGROUND OF THE INVENTION

Olanzapine is a thienobenzodiazepine that has the chemical name 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine). The chemical formula for olanzapine is $C_{17}H_{20}N_4S$, which corresponds to a molecular weight of 312.44. Olanzapine is essentially insoluble in water and is a serotonin (5-HT2) and dopamine (D1/D2) receptor antagonist that exhibits anticholinergic activity. Olanzapine has the structural formula (I):



(I)

Olanzapine is marketed in the United States under the tradename Zyprexa® and is indicated for the short-term treatment of acute manic episodes associated with bipolar disorders.

Notwithstanding the current availability of olanzapine polymorphs, salts, solvates, and hydrates described in United States Patent Nos. 6,617,321; 6,348,458; 5,736,541; and 5,703,232, the need continues to exist for olanzapine forms that evidence improved aqueous solubility and stability and thereby enable the manufacture and use of a broad range of safe and effective olanzapine pharmaceutical dosage forms. Ideally, such improved olanzapine forms: will be more stable than known olanzapine forms; will not cause discoloration of solid pharmaceutical dosage forms comprising the improved forms; and will be more water-soluble than known olanzapine forms.

SUMMARY OF THE INVENTION

The invention provides novel soluble forms of olanzapine. These forms include novel salts, co-crystals, and solvates of olanzapine. Novel olanzapine forms of the invention are stable, readily formulated, and exhibit improved aqueous solubility when compared to known olanzapine forms.

The invention also provides novel pharmaceutical compositions comprising these novel soluble forms and related methods of treatment.

Compositions and methods of the invention are useful in the treatment of psychosis and functional bowel disorders, including irritable bowel syndrome.

In one illustrative embodiment, the invention provides novel soluble olanzapine salts formed by the reaction in a crystallization solvent of olanzapine and an organic acid, preferably racemic or enatiomerically pure fumaric, maleic, and malonic acids.

In another illustrative embodiment, the invention provides solvates formed by the recrystallization, in a crystallization solvent comprising an alcohol such as methanol, of an olanzapine salt formed by the reaction of olanzapine and an organic acid.

In another illustrative embodiment, the invention provides olanzapine nicotinamide co-crystals formed by the recrystallization of olanzapine salts in a crystallization solvent comprising nicotinamide.

In another illustrative embodiment, the invention provides olanzapine glycol solvates, including olanzapine propylene glycol solvates.

In still another illustrative embodiment, the invention provides an olanzapine form formed by reacting olanzapine and a dicarboxylic acid in a heated crystallization solvent to form a reaction product, and thereafter cooling the reaction product to a temperature of between about 0° C to about 10° C over a period of about five to about fifteen hours to form the olanzapine form, wherein the olanzapine form has an aqueous solubility of between about 0.05 mg/ml to about 100 mg/ml.

These and other embodiments of the invention are described further in the detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1- PXRD diffractogram of olanzapine fumarate salt.

Figure 2- DSC thermogram of olanzapine fumarate salt.

Figure 3- PXRD diffractogram of olanzapine maleate salt.

Figure 4- DSC thermogram of olanzapine maleate salt.

Figure 5- PXRD diffractogram of olanzapine malonate salt.

Figure 6- PXRD diffractogram of olanzapine methanol solvate.

Figure 7- DSC thermogram of olanzapine methanol solvate.

Figure 8- TGA thermogram of olanzapine methanol solvate.

Figure 9- Packing diagram of olanzapine methanol solvate.

Figures 10A-B- PXRD diffractograms of a propylene glycol solvate of olanzapine.

Figure 11- DSC thermogram of a propylene glycol solvate of olanzapine.

Figure 12- TGA thermogram of a propylene glycol solvate of olanzapine.

Figure 13- Packing diagram of a propylene glycol solvate of olanzapine.

Figures 14A-B- PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form I), with the background removed and as collected, respectively.

Figure 15- DSC thermogram of a co-crystal comprising olanzapine and nicotinamide (Form I).

Figure 16- PXRD diffractogram of a co-crystal comprising olanzapine and nicotinamide (Form II).

Figures 17A-B- PXRD diffractograms of a co-crystal comprising olanzapine and nicotinamide (Form III), with the background removed and as collected, respectively.

Figures 18A-D- Packing diagrams of a co-crystal comprising olanzapine and nicotinamide (Form III).

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the following terms have the following respective meanings.

"Olanzapine" has been defined previously herein as the compound of formula (I).

"Olanzapine form (I)" and "olanzapine form (II)" mean the olanzapine forms of the same designation that are disclosed in United States Patent No. 5,703,232.

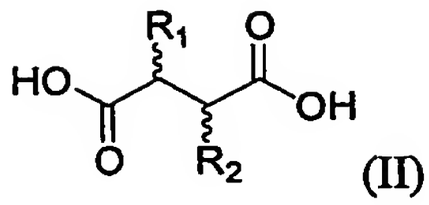
"Olanzapine forms(III)-(V)" mean the olanzapine forms of the same designation that are disclosed in United States Patent No. 6,348,458.

A "solvate" is a complex of variable stoichiometry formed by a solute (either olanzapine or salts, co-crystals, or hydrates of olanzapine) and a crystallization solvent as defined herein, including but not limited to an alcohol, preferably methanol or ethanol, naphthalene, dimethyl sulfoxide, methyl tert-butyl ether, formamide, acetonitrile, nitromethane, methylene chloride, acetic acid, pyridine, 1,4-dioxane, tetrahydrofuran, and 1,2-dichloroethane.

"Organic or inorganic acids" include, but are not limited to, carboxylic acids, dicarboxylic acids, hydrochloric acid, phosphoric acid, sulfuric acid, benzenesulfonic acid, methanesulfonic acid, and, in general terms, any acidic species that will form a thermodynamically stable crystalline (salt) form upon reaction with the free base olanzapine.

"Carboxylic acids" include, but are not limited to, formic, acetic, propionic, butyric, isobutyric, valeric, isovaleric, pivalic, caproic, caprylic, capric, lauric, myristic, palmitic, stearic, acrylic, crotonic, benzoic, cinnamic, and salicylic acids.

"Dicarboxylic acid" means a compound of formula (II):



(II)

wherein R_1 and R_2 are each independently H, OH, Cl, Br, I, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted aryl or R_1 and R_2 taken together represent a double bond as well as stereochemically pure D or L salts of a compound of formula (II).

Examples of the dicarboxylic acid of formula (II) include but are not limited to succinic acid, maleic acid, tartaric acid, malic acid or fumaric acid. Dicarboxylic acids of

formula (II) that can be used to make compounds of the invention include succinic acid, tartaric acid, malic acid, and fumaric acid. Dicarboxylic acids such as malonic acid and adipic acid can also be used. Dicarboxylic acids can be in the form of a substantially pure (R)(+) enantiomer; a substantially pure (R)(-) enantiomer; a substantially pure (S)(+) enantiomer; or a substantially pure (S)(-) enantiomer.

"Co-crystal" as used herein means a crystalline material comprised of two or more unique solids at room temperature, each containing distinctive physical characteristics, such as structure, melting point, and heats of fusion, with the exception that, if specifically stated, the API (active pharmaceutical ingredient) may be a liquid at room temperature. The co-crystals of the present invention comprise a co-crystal former H-bonded to olanzapine or a derivative thereof. The co-crystal former may be H-bonded directly to olanzapine or may be H-bonded to an additional molecule which is bound to olanzapine. The additional molecule may be H-bonded to olanzapine or bound ionically or covalently to olanzapine. The additional molecule could also be a different API. Solvates of olanzapine compounds that do not further comprise a co-crystal former are not co-crystals according to the present invention. The co-crystals may however, include one or more solvate molecules in the crystalline lattice. That is, solvates of co-crystals, or a co-crystal further comprising a solvent or compound that is a liquid at room temperature, is included in the present invention, but crystalline material comprised of only olanzapine and one or more liquids (at room temperature) are not included. Other modes of molecular recognition may also be present including, pi-stacking, guest-host complexation and van der

Waals interactions. Of the interactions listed above, hydrogen-bonding is the dominant interaction in the formation of the co-crystal, (and a required interaction according to the present invention) whereby a non-covalent bond is formed between a hydrogen bond donor of one of the moieties and a hydrogen bond acceptor of the other. Hydrogen bonding can result in several different intermolecular configurations. For example, hydrogen bonds can result in the formation of dimers, linear chains, or cyclic structures. These configurations can further include extended (two-dimensional) hydrogen bond networks and isolated triads. An alternative embodiment provides for a co-crystal wherein the co-crystal former is a second API. In another embodiment, the co-crystal former is not an API. For purposes of the present invention, the chemical and physical properties of olanzapine in the form of a co-crystal may be compared to a reference compound that is olanzapine in a different form. The reference compound may be specified as a free form, or more specifically, an anhydrate or hydrate of a free form, or more specifically, for example, a hemihydrate, monohydrate, dihydrate, trihydrate, quadrahydrate, pentahydrate; or a solvate of a free form. For example, the reference compound for olanzapine in free form co-crystallized with a co-crystal former can be olanzapine in free form. The reference compound may also be specified as crystalline or amorphous. The reference compound may also be specified as the most stable polymorph of the specified form of the reference compound.

"Soluble forms" encompass polymorphs, co-crystals, salts, hydrates, and solvates that are soluble in aqueous media at values greater than 5 μg/ml, more preferably greater than 10 μg/ml, more preferably greater than 20 μg/ml, more preferably greater than 30 μg/ml, more preferably greater than 40 μg/ml, more preferably greater than 50 μg/ml, and most preferably greater than 100 μg/ml in a solution with a pH of about 1. Preferably, the aqueous solubility is greater than 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 5.0, 10.0, 25.0, or 50.0 mg/mL, for example. Soluble multicomponent forms can comprise, for example: (a) an organic salt comprising the reaction product of olanzapine and an organic acid or an inorganic acid; and (b) one or more crystallization solvents, wherein the crystallization solvent is present in either a stoichiometric or non-stoichiometric ratio relative to the organic salt.

The term "anomer" as used herein means one of a pair of isomers of a cyclic compound resulting from creation of a new point of symmetry when a rearrangement of atoms occurs at an aldehyde or ketone position.

As used herein, the terms "stereoisomer" or "stereoisomeric form" means compounds having a stereoisomeric purity of at least 90%, and preferably at least 95% up to a stereoisomeric purity of 100% by weight, preferably compounds having a stereoisomeric purity of at least 97% up to a stereoisomeric purity of 100%, and more preferably having a stereoisomeric purity of at least 99% up to a stereoisomeric purity of 100% by weight, said weight percent based upon the total weight of the desired stereoisomers of the compound.

"Alkyl" means a straight chain or branched, saturated or unsaturated alkyl, cyclic or non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, and the like; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, and the like. Unsaturated alkyls contain at least one double or triple bond between adjacent carbon atoms (also referred to as an "alkenyl" or "alkynyl", respectively). Representative straight chain and branched alkenyls include ethylenyl, propylenyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, and the like; while representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methy1-1 butynyl, and the like. Representative saturated cyclic alkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like; while unsaturated cyclic alkyls include cyclopentenyl and cyclohexenyl, and the like. Cycloalkyls are also referred to herein as "carbocyclic" rings systems, and include bi- and tri-cyclic ring systems having from 8 to 14 carbon atoms such as a cycloalkyl (such as cyclopentane or cyclohexane) fused to one or more aromatic (such as phenyl) or non-aromatic (such as cyclohexane) carbocyclic rings.

As used herein, the term "aryl" means a carbocyclic or heterocyclic aromatic group containing from 5 to 10 ring atoms. The ring atoms of a carbocyclic aromatic group are all carbon atoms, and include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. A carbocyclic aromatic group can be unsubstituted or substituted. Preferably, the carbocyclic aromatic group

is a phenyl group. The ring atoms of a heterocyclic aromatic group contains at least one heteroatom, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Illustrative examples of heterocyclic aromatic groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phienyl, isoxazolyl, indolyl, oxetanyl, azepinyl, piperazinyl, morpholinyl, dioxanyl, thietanyl and oxazolyl. A heterocyclic aromatic group can be unsubstituted or substituted. Preferably, a heterocyclic aromatic is a monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms.

"Halo" and "halogen" are used in the conventional sense to refer to a chloro, bromo, fluoro or iodo substituent.

The term "substituted" as used herein means any of the above groups (*i.e.*, aryl or alkyl or halogen) wherein at least one hydrogen atom is replaced with a substituent. In the case of a keto substituent (C=O) two hydrogen atoms are replaced. Substituents include halogen, hydroxy, alkyl, aryl, arylalkyl, heterocycle or heterocyclealkyl.

As used herein, the term "adjunctively administered" refers to the administration of one or more compounds or active ingredients in addition to pharmaceutical composition of the invention, either simultaneously with the same or at intervals prior to, during, or following administration of the pharmaceutical composition, to achieve the desired therapeutic or prophylactic effect.

A "polymorph" is a particular crystalline form of an organic compound that exists in a variety of crystal structures. While polymorphic modifications have the same chemical composition, they differ in packing, geometrical arrangement, and other descriptive properties of the crystalline solid state. As such, these modifications may have different solid-state physical properties such as shape, color density, hardness, deformability, stability, and dissolution properties.

As used herein, the term"pharmaceutically acceptable salt" refers to a salt prepared from pharmacologically acceptable anions, which include but are not limited to anions such as hydrochloride, phosphate, formate, oxalate, adipate, succinate, fumarate, malate, tartrate, malonate, maleate, mesylate and benzenesulfonate. Pharmacologically acceptable anions also include, but are not limited to, oxalate, tartrate, benzenesulfonate, malate and succinate, hydrobromide, bitartrate, para-toluenesulfonate, glycolate, glucuronate, mucate, gentisate, isonicotinate, saccharate,

acid phosphate, hydroiodide, nitrate, sulfate, bisulfate, acetate, propionate, camphorsulfonate, gluconate, isothionate, lactate, furoate, glutamate, ascorbate, benzoate, anthranilate, salicylate, phentylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, pantothenate, stearate, sulfanilate, alginate, p-toluenesulfonate, mesylate, and galacturonate.

"Crystallization solvents" include aromatic hydrocarbons, C_3 –C_9 ketones, C_3 –C_9 branched alcohols, C_3 –C_9 esters, C_5 –C_9 hydrocarbons, C_3 –C_9 ethers, and cyclic ethers. Aromatic hydrocarbons used as crystallization solvents include C_4 –C_6 alkyl aromatic solvents which may include substituted aromatics. Examples of aromatic hydrocarbons include, but are not limited to toluene, benzene, and the like. The term "C_5 –C_9 hydrocarbons" refer to C_5 –C_9 alkyl solvents which may be substituted, branched or unbranched alkyl. Such hydrocarbon solvents include, but are not limited to straight or branched heptane, octane, pentane, and the like. The term "C_3 –C_9 ketones" refers to straight or branched ketones which may optionally be substituted. The term "C_3 –C_9 esters" refers to straight or branched esters which may optionally be substituted. The term "ethers" refer to lower alkyl (C_2 –C_8) alkyl ethers which may be straight, branched or substituted. The term ether shall include but is not limited to, for example, t-butyl methylether, and the like. The term "cyclic ether" includes C_5 –C_7 cyclic ether which may be optionally substituted. It is especially preferred that the ether solvent is dry. It is particularly preferred that such dry solvent shall contain less than about 1% water. Urea and urea derivatives can also be used as crystallization solvents.

Preferred crystallization solvents are selected on the basis that olanzapine must be at least partially soluble in the solvent selected, and the solvent selected must not form a solvate with olanzapine. Most preferably, the solvate dissolves in the solvent before the crystallization process is begun.

Preferred crystallization solvents used in making olanzapine forms include 1,4-dioxane ("dioxane"), 1,2-dichloroethane, dimethoxyethane, glycols including ethylene glycol and diethylene glycol, dimethyl ether, tetrahydrofuran (THF), isopropyl acetate, diisopropyl ether, hexane, heptane, cyclohexane, toluene or xylene, alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, and tert-butanol, ketones such as methyl ethyl ketone or isobutyl methyl ketone, amides such as dimethylformamide, dimethylacetamide or N-methylpyrrolidone, pyridine, DMSO, xylene, urea or urea derivatives, acetic acid, and mixtures thereof. Preferred

crystallization solvents include 1, 2-dichloroethane, propylene glycol, and isopropyl acetate.

"Urea Derivative" means the reaction product of an isocyanate of the formula R-N=C=O with an amine of the formula $R'NH_2$, where R and R' are the same or different and are a substituted or unsubstituted C_{1-5} alkyl, C_{1-5} alkenyl, or C_{1-5} alkynyl.

"Glycols" include, but are not limited to, ethylene glycol, 1, 3-propane diol, propylene glycol, glycol ethers including dipropylene glycolpropyl ether, dipropylene glycolbutyl ether, and diethylene glycol butyl ether.

The term "patient" is used throughout the specification to describe an animal, preferably a human, to whom treatment, including prophylactic treatment, with the compositions according to the present invention is provided. For treatment of those infections, conditions or disease states which are specific for a specific animal such as a human patient, the term patient refers to that specific animal.

The terms "an effective amount", "therapeutic effective amount", or "therapeutically effective amount" shall mean an amount or concentration of a composition according to the present invention which is effective within the context of its administration or use, including, for example, the treatment of bipolar disorders. Thus, the term "effective amount" is used throughout the specification to describe concentrations or amounts of compounds according to the present invention which may be used to produce a favorable change in the disease or condition treated, whether that change is the control of acute manic episodes associated with bipolar disorders or another favorable psychiatric or physiological result.

The novel soluble olanzapine forms of the invention are reasonably considered to exhibit activity at the 5-HT-2 receptor and 5-HT1C receptor. Compositions of the invention are reasonably considered to be effective in the treatment of psychotic conditions but less likely to induce extra pyramidal side-effects.

As used herein the term "psychosis" shall mean pathologic psychological conditions which are psychoses or may be associated with psychotic features including, but not limited to the following disorders which have been characterized in the DSM-III-R. Diagnostic and Statistical Manual of Mental Disorders, Revised, 3rd Ed. (1980). The DSM-III-R was prepared by the Task Force on Nomenclature and Statistics of the American Psychiatric Association, and provides clear descriptions of diagnostic categories. The numbers in parenthesis refer to the DSM-III-R categories. The skilled artisan will recognize that there are alternative nomenclatures and

classification systems for pathologic psychological conditions and that these systems evolve with medical scientific progress.

Examples of conditions which may be treated using compositions of the invention include, but are not limited to, Conduct Disorder, Group Type (312.20), Conduct Disorder, Solitary Aggressive Type (312.00), Conduct Disorder, Undifferentiated Type (312.90), Tourette's Disorder (307.23), Chronic Motor Or Vocal Tic Disorder (307.22), Transient Tic Disorder (307.21), Tic Disorder NOS (307.20), Multi-infarct dementia, with Delirium (290.41), Multi-infarct dementia, with Delusions (290.42), Multi-infarct dementia, with Depression (290.43), Multi-infarct dementia, Uncomplicated (290.40), Senile Dementia NOS (290.00), Presenile Dementia NOS (290.10), Alcohol Withdrawal Delirium (291.00), Alcohol Hallucinosis (291.30), Alcohol Dementia Associated with Alcoholism (291.20), Amphetamine or Similarly Acting Sympathomimetic Intoxication (305.70), Amphetamine or Similarly Acting Sympathomimetic Delirium (292.81), Amphetamine or Similarly Acting Sympathomimetic Delusional Disorder (292.11), Cannabis Delusional Disorder (292.11), Cocaine Intoxication (305.60), Cocaine Delirium (292.81), Cocaine Delusional Disorder (292.11), Hallucinogen Hallucinosis (305.30), Hallucinogen Delusional Disorder (292.11), Hallucinogen Mood Disorder (292.84), Hallucinogen Posthallucinogen Perception Disorder (292.89), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Intoxication (305.90), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delirium (292.81), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Delusional Disorder (292.11), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Mood Disorder (292.84), Phencyclidine (PCP) or Similarly Acting Arylcyclohexylamine Organic Mental Disorder NOS (292.90), Other or Unspecified Psychoactive Substance Intoxication (305.90), Other or Unspecified Psychoactive Substance Delirium (292.81), Other or Unspecified Psychoactive Substance Dementia (292.82), Other or Unspecified Psychoactive Substance Delusional Disorder (292.11), Other or Unspecified Psychoactive Substance Hallucinosis (292.12), Other or Unspecified Psychoactive Substance Mood Disorder (292.84), Other or Unspecified Psychoactive Substance Anxiety Disorder (292.89), Other or Unspecified Psychoactive Substance Personality Disorder (292.89), Other or Unspecified Psychoactive Substance Organic Mental Disorder NOS (292.90), Delirium (293.00), Dementia (294.10), Organic Delusional Disorder (293.81), Organic Hallucinosis (293.82), Organic Mood Disorder

(293.83), Organic Anxiety Disorder (294.80), Organic Mental Disorder (294.80), Obsessive Compulsive Disorder (300.30), Post-traumatic Stress Disorder (309.89), Generalized Anxiety Disorder (300.02), Anxiety Disorder NOS (300.00), Body Dysmorphic Disorder (300.70), Hypochondriasis (or Hypochondriacal Neurosis) (300.70), Somatization Disorder (300.81), Undifferentiated Somatoform Disorder (300.70), Somatoform Disorder NOS (300.70), Intermittent Explosive Disorder (312.34), Kleptomania (312.32), Pathological Gambling (312.31), Pyromania (312.33), Trichotillomania (312.39), and Impulse Control Disorder NOS (312.39). Schizophrenia, Catatonic, Subchronic, (295.21), Schizophrenia, Catatonic, Chronic (295.22), Schizophrenia, Catatonic, Subchronic with Acute Exacerbation (295.23), Schizophrenia, Catatonic, Chronic with Acute Exacerbation (295.24), Schizophrenia, Catatonic, in Remission (295.55), Schizophrenia, Catatonic, Unspecified (295.20), Schizophrenia, Disorganized, Subchronic (295.11), Schizophrenia, Disorganized, Chronic (295.12), Schizophrenia, Disorganized, Subchronic with Acute Exacerbation (295.13), Schizophrenia, Disorganized, Chronic with Acute Exacerbation (295.14), Schizophrenia, Disorganized, in Remission (295.15), Schizophrenia, Disorganized, Unspecified (295.10), Schizophrenia, Paranoid, Subchronic (295.31), Schizophrenia, Paranoid, Chronic (295.32), Schizophrenia, Paranoid, Subchronic with Acute Exacerbation (295.33), Schizophrenia, Paranoid, Chronic with Acute Exacerbation (295.34), Schizophrenia, Paranoid, in Remission (295.35), Schizophrenia, Paranoid, Unspecified (295.30), Schizophrenia, Undifferentiated, Subchronic (295.91), Schizophrenia, Undifferentiated, chronic (295.92), Schizophrenia, Undifferentiated, Subchronic with Acute Exacerbation (295.93), Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation (295.94), Schizophrenia, Undifferentiated, in Remission (295.95), Schizophrenia, Undifferentiated, Unspecified (295.90), Schizophrenia, Residual, Subchronic (295.61), Schizophrenia, Residual, Chronic (295.62), Schizophrenia, Residual, Subchronic with Acute Exacerbation (295.63), Schizophrenia, Residual, Chronic with Acute Exacerbation (295.94), Schizophrenia, Residual, in Remission (295.65), Schizophrenia, Residual, Unspecified (295.60), Delusional (Paranoid) Disorder (297.10), Brief Reactive Psychosis (298.80), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), Induced Psychotic Disorder (297.30), Psychotic Disorder NOS (Atypical Psychosis) (298.90), Bipolar Disorder, Mixed, Severe, without Psychotic Features (296.63), Bipolar Disorder, Manic, Severe, without Psychotic Features (296.43), Bipolar Disorder,

Depressed, Severe, without Psychotic Features (296.53), Major Depression, Single Episode, Severe, without Psychotic Features (296.23), Major Depression, Recurrent, Severe, without Psychotic Features (296.33), Bipolar Disorder, Mixed, with Psychotic Features (296.64), Bipolar Disorder, Manic, with Psychotic Features (296.44), Bipolar Disorder, Depressed, with Psychotic Features (296.54), Bipolar Disorder NOS (296.70), Major Depression, Single Episode, with Psychotic Features (296.24), and Major Depression, Recurrent with Psychotic Features (296.34).

Preferably, an effective amount of a composition of the invention is used for the treatment of Tourette's Disorder; Schizophrenia, Catatonic, Subchronic; Schizophrenia, Catatonic, Chronic; Schizophrenia, Catatonic, Subchronic with Acute Exacerbation; Schizophrenia, Catatonic, Chronic with Acute Exacerbation; Schizophrenia, Catatonic, in Remission; Schizophrenia, Catatonic, Unspecified; Schizophrenia, Disorganized, Subchronic; Schizophrenia, Disorganized, Chronic; Schizophrenia, Disorganized, Subchronic with Acute Exacerbation; Schizophrenia, Disorganized, Chronic with Acute Exacerbation; Schizophrenia, Disorganized, in Remission; Schizophrenia, Disorganized, Unspecified; Schizophrenia, Paranoid, Subchronic; Schizophrenia, Paranoid, Chronic; Schizophrenia, Paranoid, Subchronic with Acute Exacerbation; Schizophrenia, Paranoid, Chronic with Acute Exacerbation; Schizophrenia, Paranoid, in Remission; Schizophrenia, Paranoid, Unspecified; Schizophrenia, Undifferentiated, Subchronic; Schizophrenia, Undifferentiated, Chronic; Schizophrenia, Undifferentiated, Subchronic with Acute Exacerbation; Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation; Schizophrenia, Undifferentiated, in Remission; Schizophrenia, Undifferentiated, Unspecified; Schizophrenia, Residual, Subchronic; Schizophrenia, Residual, Chronic; Schizophrenia, Residual, Subchronic with Acute Exacerbation; Schizophrenia, Residual, Chronic with Acute Exacerbation; Schizophrenia, Residual, in Remission; Schizophrenia, Residual, Unspecified; Delusional (Paranoid) Disorder; Brief Reactive Psychosis; Schizophreniform Disorder; Schizoaffective Disorder; Induced Psychotic Disorder; Psychotic Disorder NOS (Atypical Psychosis); Bipolar Disorder, Mixed, with Psychotic Features; Bipolar Disorder, Manic, with Psychotic Features; Bipolar Disorder, Depressed, with Psychotic Features; Bipolar Disorder NOS; Major Depression, Single Episode, with Psychotic Features; Hebephrenic Schizophrenia; Post-Schizophrenic Depression; Delusional Disorder; and Other Persistent Delusional Disorders.

More preferably, an effective amount of a composition of the invention is used to treat the following pathologic psychological conditions including Schizophrenia, Catatonic, Subchronic; Schizophrenia, Catatonic, Chronic; Schizophrenia, Catatonic, Subchronic with Acute Exacerbation; Schizophrenia, Catatonic, Chronic with Acute Exacerbation; Schizophrenia, Catatonic, in Remission; Schizophrenia, Catatonic, Unspecified; Schizophrenia, Disorganized, Subchronic; Schizophrenia, Disorganized, Chronic; Schizophrenia, Disorganized, Subchronic with Acute Exacerbation; Schizophrenia, Disorganized, Chronic with Acute Exacerbation; Schizophrenia, Disorganized, in Remission; Schizophrenia, Disorganized, Unspecified; Schizophrenia, Paranoid, Subchronic; Schizophrenia, Paranoid, Chronic; Schizophrenia, Paranoid, Subchronic with Acute Exacerbation; Schizophrenia, Paranoid, Chronic with Acute Exacerbation; Schizophrenia, Paranoid, in Remission; Schizophrenia, Paranoid, Unspecified; Schizophrenia, Undifferentiated, Subchronic; Schizophrenia, Undifferentiated, Chronic; Schizophrenia, Undifferentiated, Subchronic with Acute Exacerbation; Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation; Schizophrenia, Undifferentiated, in Remission; Schizophrenia, Undifferentiated, Unspecified; Schizophrenia, Residual, Subchronic; Schizophrenia, Residual, Chronic; Schizophrenia, Residual, Subchronic with Acute Exacerbation; Schizophrenia, Residual, Chronic with Acute Exacerbation; Schizophrenia, Residual, in Remission; Schizophrenia, Residual, Unspecified; Delusional (Paranoid) Disorder; Brief Reactive Psychosis; Schizophreniform Disorder; Schizoaffective Disorder; Induced Psychotic Disorder; Psychotic Disorder NOS (Atypical Psychosis);Bipolar Disorder, Mixed, with Psychotic Features; Bipolar Disorder, Manic, with Psychotic Features; Bipolar Disorder, Depressed, with Psychotic Features; Bipolar Disorder NOS; Major Depression, Single Episode, with Psychotic Features; Hebephrenic Schizophrenia; Post-Schizophrenic Depression; Delusional Disorder; and Other Persistent Delusional Disorders.

Examples of conditions which are most preferably treated using an effective amount of a composition of the invention include Schizophrenia, Catatonic, Subchronic; Schizophrenia, Catatonic, Chronic; Schizophrenia, Catatonic, Subchronic with Acute Exacerbation; Schizophrenia, Catatonic, Chronic with Acute Exacerbation; Schizophrenia, Catatonic, in Remission; Schizophrenia, Catatonic, Unspecified; Schizophrenia, Disorganized, Subchronic; Schizophrenia, Disorganized, Chronic; Schizophrenia, Disorganized, Subchronic with Acute Exacerbation;

Schizophrenia, Disorganized, Chronic with Acute Exacerbation; Schizophrenia, Disorganized, in Remission; Schizophrenia, Disorganized, Unspecified; Schizophrenia, Paranoid, Subchronic; Schizophrenia, Paranoid, Chronic; Schizophrenia, Paranoid, Subchronic with Acute Exacerbation; Schizophrenia, Paranoid, Chronic with Acute Exacerbation; Schizophrenia, Paranoid, in Remission; Schizophrenia, Paranoid, Unspecified; Schizophrenia, Undifferentiated, Subchronic; Schizophrenia, Undifferentiated, Chronic; Schizophrenia, Undifferentiated, Subchronic with Acute Exacerbation; Schizophrenia, Undifferentiated, Chronic with Acute Exacerbation; Schizophrenia, Undifferentiated, in Remission; Schizophrenia, Undifferentiated, Unspecified; Schizophrenia, Residual, Subchronic; Schizophrenia, Residual, Chronic; Schizophrenia, Residual, Subchronic with Acute Exacerbation; Schizophrenia, Residual, Chronic with Acute Exacerbation; Schizophrenia, Residual, in Remission; Schizophrenia, Residual, Unspecified; Delusional (Paranoid) Disorder; Brief Reactive Psychosis; Schizophreniform Disorder; Schizoaffective Disorder; and Hebephrenic Schizophrenia.

Examples of anxiety disorders which may more preferably be treated using an effective amount of an effective amount of a composition of the invention include Psychoactive Substance Anxiety Disorder; Organic Anxiety Disorder; Obsessive Compulsive Disorder; Post-traumatic Stress Disorder; Generalized Anxiety Disorder; and Anxiety Disorder NOS.

Examples of the anxiety disorders which are most preferably treated using an effective amount of a composition of the invention include Organic Anxiety Disorder; Obsessive Compulsive Disorder; Post-traumatic Stress Disorder; Generalized Anxiety Disorder; and Anxiety Disorder NOS.

As used herein the term "Functional Bowel Disorder" refers to a functional gastrointestinal disorder manifested by (1) abdominal pain and/or (2) symptoms of disturbed defecation (urgency, straining, feeling of incomplete evacuation, altered stool form , consistency, and altered bowel frequency/timing) and/or (3) bloating (distention). The term "Functional Bowel Disorder" includes but is not limited to irritable bowel syndrome, hypermotility, ichlasia, hypertonic lower esophogeal sphinctor, tachygastria, constipation, hypermotility associated with irritable bowel syndrome.

Functional Bowel Disorders are characterized by abnormal bowel function without detectable structural abnormalities. Abnormal bowel function includes

diarrhea, constipation, mucorrhea, and pain or discomfort over the course of the sigmoid colon. Such disorders are influenced by psychological factors and stressful life situations.

The Functional Bowel Disorder, Irritable Bowel Syndrome (IBS), is one of the most commonly encountered gastrointestinal disorders. Between 20% and 50% of patients referred to gastrointestinal clinics suffer from IBS. Symptoms of IBS occur in approximately 14% of otherwise apparently healthy people. IBS is a complex condition, in part because it is not a disease but a syndrome composed of a number of conditions with similar manifestations.

An effective amount of a composition of the invention may exhibit antimuscarinic activity, 5-HT2B receptor activity, and may be denoted for use in the treatment of certain gastrointestinal conditions. Thus, the compound is suggested for the treatment of Functional Bowel Disorders including, but not limited to, irritable bowel syndrome, gastric hypermotility, and related conditions.

Insofar as gastrointestinal treatments are concerned, an effective amount of a composition of the invention is preferably used for the treatment of irritable bowel syndrome or gastric hypermotility disorder.

Pharmaceutical Compositions and Dosage Forms

Pharmaceutical dosage forms of the invention can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. Oral and parenteral pharmaceutical compositions and dosage forms are a preferred dosage form. Preferably, the oral dosage form is a solid dosage form, such as a tablet, a caplet, a hard gelatin capsule, a starch capsule, a hydroxypropyl methylcellulose ("HPMC") capsule, or a soft elastic gelatin capsule. parenteral pharmaceutical compositions and dosage forms. Other preferred dosage forms include an intradermal dosage form, an intramuscular dosage form, a subcutaneous dosage form, and an intravenous dosage form.

Pharmaceutical compositions and dosage forms of the invention comprise a novel pharmaceutically acceptable olanzapine form, e.g., novel solvates, co-crystals, or salts of olanzapine. Pharmaceutical compositions and unit dosage forms of the invention typically also comprise one or more pharmaceutically acceptable excipients or diluents. In one embodiment, the pharmaceutical compositions and unit dosage

forms of the invention typically also comprise one or more pharmaceutically acceptable excipients or diluents, wherein at least one of the pharmaceutically acceptable excipients or diluents is an antioxidant.

Pharmaceutical unit dosage forms of this invention are suitable for oral, mucosal (e.g., nasal, sublingual, vaginal, buccal, or rectal), parenteral (e.g., intramuscular, subcutaneous, intravenous, intraarterial, or bolus injection), topical, or transdermal administration to a patient. Examples of dosage forms include, but are not limited to: tablets; caplets; capsules, such as hard gelatin capsules, starch capsules, hydroxypropyl methylcellulose ("HPMC") capsules, and soft elastic gelatin capsules; cachets; troches; lozenges; dispersions; suppositories; ointments; cataplasms (poultices); pastes; powders; dressings; creams; plasters; solutions; patches; aerosols (e.g., nasal sprays or inhalers); gels; liquid dosage forms suitable for oral or mucosal administration to a patient, including suspensions (e.g., aqueous or non-aqueous liquid suspensions, oil-in-water emulsions, or water-in-oil liquid emulsions), solutions, and elixirs; liquid dosage forms suitable for parenteral administration to a patient; and sterile solids (e.g., crystalline or amorphous solids) that can be reconstituted to provide liquid dosage forms suitable for parenteral administration to a patient.

The composition, shape, and type of dosage forms of the invention will typically vary depending on their use. For example, a dosage form used in the acute treatment of a disease or disorder may contain larger amounts of the active ingredient than a dosage form used in the chronic treatment of the same disease or disorder. Similarly, a parenteral dosage form may contain smaller amounts of the active ingredient than an oral dosage form used to treat the same disease or disorder. These and other ways in which specific dosage forms encompassed by this invention will vary from one another will be readily apparent to those skilled in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton PA (1990) or Remington: The Science and Practice of Pharmacy, 19th ed., Mack Publishing, Easton PA (1995).

Typical pharmaceutical compositions and dosage forms comprise one or more excipients. Suitable excipients are well known to those skilled in the art of pharmacy, and non-limiting examples of suitable excipients are provided herein. Whether a particular excipient is suitable for incorporation into a pharmaceutical composition or dosage form depends on a variety of factors well known in the art including, but not limited to, the way in which the dosage form will be administered to a patient. For

example, oral dosage forms such as tablets or capsules may contain excipients not suited for use in parenteral dosage forms. In addition, pharmaceutical compositions or dosage forms may contain one or more compounds that reduce or alter the rate by which the active ingredient will decompose. Such compounds, which are referred to herein as "stabilizers", include, but are not limited to, antioxidants, pH buffers, or salt buffers.

One or more antioxidants can be used in pharmaceutical compositions and dosage forms to deter radical oxidation of the active ingredient, wherein such antioxidants include, but are not limited to, ascorbic acid, phenolic antioxidants including, but not limited to, butylated hydroxyanisole (BHA) and propyl gallate, and chelators including, but not limited to citrate, EDTA, and DTPA. Preferably, in cases where radical oxidation of the active ingredient is known to occur, a combination of phenolic antioxidants and chelators can be used.

Like the amounts and types of excipients, the amounts and specific type of active ingredient in a dosage form may differ depending on factors such as, but not limited to, the route by which it is to be administered to patients. However, typical dosage forms of the invention comprise an olanzapine form, for example a novel pharmaceutically acceptable crystal, co-crystal, or solvate of olanzapine in an amount of from about 10 mg to about 1000 mg, preferably in an amount of from about 25 mg to about 500 mg, more preferably in an amount of from 40 mg to 400 mg, and most preferably in an amount of from about 50 mg to about 200 mg.

Oral Dosage Forms

Pharmaceutical compositions of the invention that are suitable for oral administration can be presented as discrete dosage forms, such as, but not limited to, tablets (including without limitation scored or coated tablets), pills, caplets, capsules (including without limitation hard gelatin capsules, starch capsules, HPMC capsules, and soft elastic gelatin capsules), chewable tablets, powder packets, sachets, troches, wafers, aerosol sprays, or liquids, such as but not limited to, syrups, elixirs, solutions or suspensions in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil emulsion. Such compositions contain a predetermined amount of the active ingredient, and may be prepared by methods of pharmacy well known to those skilled in the art. See generally, Remington's Pharmaceutical Sciences, 18th ed.,

Mack Publishing, Easton PA (1990) or Remington: The Science and Practice of Pharmacy, 19th ed., Mack Publishing, Easton PA (1995).

Typical oral dosage forms of the invention are prepared by combining the active ingredient in an intimate admixture with at least one excipient according to conventional pharmaceutical compounding techniques. Excipients can take a wide variety of forms depending on the form of the composition desired for administration. For example, excipients suitable for use in oral liquid or aerosol dosage forms include, but are not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents. Examples of excipients suitable for use in solid oral dosage forms (e.g., powders, tablets, capsules, and caplets) include, but are not limited to, starches, sugars, microcrystalline cellulose, kaolin, diluents, granulating agents, lubricants, binders, stabilizers, and disintegrating agents.

Due to their ease of administration, tablets, caplets, and capsules (such as hard gelatin, HPMC, or starch capsules) represent the most advantageous solid oral dosage unit forms, in which case solid pharmaceutical excipients are used. If desired, tablets or caplets can be coated by standard aqueous or nonaqueous techniques. These dosage forms can be prepared by any of the methods of pharmacy. In general, pharmaceutical compositions and dosage forms are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary.

For example, a tablet can be prepared by compression or molding. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient(s) in a free-flowing form, such as a powder or granules, optionally mixed with one or more excipients. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

Examples of excipients that can be used in oral dosage forms of the invention include, but are not limited to, binders, stabilizers, fillers, disintegrants, and lubricants. Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch,

hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof.

Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL-PH-101, AVICEL-PH-103, AVICEL RC-581, and AVICEL-PH-105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, PA, U.S.A.), and mixtures thereof. An exemplary suitable binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose sold as AVICEL RC-581. Suitable anhydrous or low moisture excipients or additives include AVICEL-PH-103™ and Starch 1500 LM.

Examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. The binder or filler in pharmaceutical compositions of the invention is typically present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Disintegrants can be used in the pharmaceutical compositions and dosage forms to provide tablets or caplets that disintegrate when exposed to an aqueous environment. Tablets or caplets that contain too much disintegrant may disintegrate in storage, while those that contain too little may be insufficient for disintegration to occur and may thus alter the rate and extent of release of the active ingredient(s) from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) should be used to form solid oral dosage forms of the invention. The amount of disintegrant used varies based upon the type of formulation and mode of administration, and is readily discernible to those of ordinary skill in the art. Typical pharmaceutical compositions comprise from about 0.5 to about 15 weight percent of disintegrant, preferably from about 1 to about 5 weight percent of disintegrant.

Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums, and mixtures thereof.

Antioxidants can be used in the pharmaceutical compositions and dosage forms to deter degradation or radical oxidation of the active ingredient. Examples of suitable antioxidants include, but are not limited to, ascorbic acid, phenolic antioxidants including, but not limited to, butylated hydroxyanisole (BHA) and propyl gallate, and chelators including, but not limited to, citrate, EDTA, and DTPA, or combinations thereof.

Lubricants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, MD), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, TX), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, MA), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms into which they are incorporated.

Other oral dosage forms for pharmaceutical compositions of the invention are soft elastic gelatin capsules. Soft elastic gelatin capsule unit dosage forms can be made using conventional methods well known in the art. See, e.g., Ebert, Pharm. Tech, 1(5):44-50 (1977). In general, soft elastic gelatin capsules (also known as "soft gels") have an elastic or soft, globular or oval shaped gelatin shell that is typically a bit thicker than that of hard gelatin capsules, wherein a plasticizing agent, e.g., glycerin, sorbitol, or a similar polyol, is added to a gelatin. The type of gelatin, as well as the amounts of plasticizer and water, can be used to vary the hardness of the capsule shell. The soft gelatin shells may contain a preservative, such as methyl- and propylparabens and sorbic acid, to prevent the growth of fungi. The active ingredient may be dissolved or suspended in a liquid vehicle or carrier, such as vegetable or mineral oils, glycols, such as polyethylene glycol and propylene glycol, triglycerides, surfactants, such as polysorbates, or a combination thereof.

Controlled and Delayed Release Dosage Forms

Pharmaceutically acceptable salts, co-crystals, and solvates of olanzapine can be administered by controlled- or delayed-release means. Controlled-release pharmaceutical products have a common goal of improving drug therapy over that achieved by their non-controlled release counterparts. Ideally, the use of an optimally designed controlled-release preparation in medical treatment is characterized by a minimum of drug substance being employed to cure or control the condition in a minimum amount of time. Advantages of controlled-release formulations include: 1) extended activity of the drug; 2) reduced dosage frequency; 3) increased patient compliance; 4) usage of less total drug; 5) reduction in local or systemic side effects; 6) minimization of drug accumulation; 7) reduction in blood level fluctuations; 8) improvement in efficacy of treatment; 9) reduction of potentiation or loss of drug activity; and 10) improvement in speed of control of diseases or conditions. (Kim, Cherng-ju, Controlled Release Dosage Form Design, 2 Technomic Publishing, Lancaster, Pa.: 2000).

Conventional dosage forms generally provide rapid or immediate drug release from the formulation. Depending on the pharmacology and pharmacokinetics of the drug, use of conventional dosage forms can lead to wide fluctuations in the concentrations of the drug in a patient's blood and other tissues. These fluctuations can impact a number of parameters, such as dose frequency, onset of action, duration of efficacy, maintenance of therapeutic blood levels, toxicity, side effects, and the like. Advantageously, controlled-release formulations can be used to control a drug's onset of action, duration of action, plasma levels within the therapeutic window, and peak blood levels. In particular, controlled- or extended-release dosage forms or formulations can be used to ensure that the maximum effectiveness of a drug is achieved while minimizing potential adverse effects and safety concerns, which can occur both from under dosing a drug (i.e., going below the minimum therapeutic levels) as well as exceeding the toxicity level for the drug.

Most controlled-release formulations are designed to initially release an amount of drug (active ingredient) that promptly produces the desired therapeutic effect, and gradually and continually release other amounts of drug to maintain this level of therapeutic or prophylactic effect over an extended period of time. In order to maintain this constant level of drug in the body, the drug must be released from the dosage form at a rate that will replace the amount of drug being metabolized and

excreted from the body. Controlled-release of an active ingredient can be stimulated by various conditions including, but not limited to, pH, ionic strength, osmotic pressure, temperature, enzymes, water, and other physiological conditions or compounds.

A variety of known controlled- or extended-release dosage forms, formulations, and devices can be adapted for use with the olanzapine forms and compositions of the invention. Examples include, but are not limited to, those described in U.S. Pat. Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; 4,008,719; 5,674,533; 5,059,595; 5,591,767; 5,120,548; 5,073,543; 5,639,476; 5,354,556; 5,733,566; and 6,365,185 B1; each of which is incorporated herein by reference. These dosage forms can be used to provide slow or controlled-release of one or more active ingredients using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems (such as OROS® (Alza Corporation, Mountain View, Calif. USA)), multilayer coatings, microparticles, liposomes, or microspheres or a combination thereof to provide the desired release profile in varying proportions. Additionally, ion exchange materials can be used to prepare immobilized, adsorbed salt forms of olanzapine and thus effect controlled delivery of the drug. Examples of specific anion exchangers include, but are not limited to, Duolite® A568 and Duolite® AP143 (Rohm & Haas, Spring House, PA. USA).

One embodiment of the invention encompasses a unit dosage form which comprises a pharmaceutically acceptable salt of olanzapine (e.g., a fumarate, maleate, or malonate salt), or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof, and one or more pharmaceutically acceptable excipients or diluents, wherein the pharmaceutical composition or dosage form is formulated for controlled-release. Specific dosage forms utilize an osmotic drug delivery system.

A particular and well-known osmotic drug delivery system is referred to as OROS® (Alza Corporation, Mountain View, Calif. USA). This technology can readily be adapted for the delivery of compounds and compositions of the invention. Various aspects of the technology are disclosed in U.S. Pat. Nos. 6,375,978 B1; 6,368,626 B1; 6,342,249 B1; 6,333,050 B2; 6,287,295 B1; 6,283,953 B1; 6,270,787 B1; 6,245,357 B1; and 6,132,420; each of which is incorporated herein by reference. Specific adaptations of OROS® that can be used to administer compounds and

compositions of the invention include, but are not limited to, the OROS® Push-Pull™, Delayed Push-Pull™, Multi-Layer Push-Pull™, and Push-Stick™ Systems, all of which are well known. See, e.g., http://www.alza.com. Additional OROS® systems that can be used for the controlled oral delivery of compounds and compositions of the invention include OROS®-CT and L-OROS®. Id.; see also, Delivery Times, vol. II, issue II (Alza Corporation).

Conventional OROS® oral dosage forms are made by compressing a drug powder into a hard tablet, coating the tablet with cellulose derivatives to form a semi-permeable membrane, and then drilling an orifice in the coating (e.g., with a laser). (Kim, Cherng-ju, Controlled Release Dosage Form Design, 231-238 Technomic Publishing, Lancaster, Pa.: 2000). The advantage of such dosage forms is that the delivery rate of the drug is not influenced by physiological or experimental conditions. Even a drug with a pH-dependent solubility can be delivered at a constant rate regardless of the pH of the delivery medium. But because these advantages are provided by a build-up of osmotic pressure within the dosage form after administration, conventional OROS® drug delivery systems cannot be used to effectively deliver drugs with low water solubility. Because olanzapine salts, co-crystals, solvates, and complexes of this invention are far more soluble in water than olanzapine itself, they are well suited for osmotic-based delivery to patients. This invention does, however, encompass the incorporation of olanzapine, and non-salt isomers and isomeric mixtures thereof, into OROS® dosage forms.

A specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a dry or substantially dry state drug layer located within the cavity adjacent to the exit orifice and in direct or indirect contacting relationship with the expandable layer; and a flow-promoting layer interposed between the inner surface of the wall and at least the external surface of the drug layer located within the cavity, wherein the drug layer comprises a salt, co-crystal, or solvate of olanzapine, or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,368,626, the entirety of which is incorporated herein by reference.

Another specific dosage form of the invention comprises: a wall defining a cavity, the wall having an exit orifice formed or formable therein and at least a portion of the wall being semipermeable; an expandable layer located within the cavity remote from the exit orifice and in fluid communication with the semipermeable portion of the wall; a drug layer located within the cavity adjacent the exit orifice and in direct or indirect contacting relationship with the expandable layer; the drug layer comprising a liquid, active agent formulation absorbed in porous particles, the porous particles being adapted to resist compaction forces sufficient to form a compacted drug layer without significant exudation of the liquid, active agent formulation, the dosage form optionally having a placebo layer between the exit orifice and the drug layer, wherein the active agent formulation comprises a salt, co-crystal, or solvate of olanzapine, or a polymorph, solvate, hydrate, dehydrate, co-crystal, anhydrous, or amorphous form thereof. See U.S. Pat. No. 6,342,249, the entirety of which is incorporated herein by reference.

Topical Dosage Forms

Topical dosage forms of the invention include, but are not limited to, creams, lotions, ointments, gels, shampoos, sprays, aerosols, solutions, emulsions, and other forms known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia, PA (1985). For non-sprayable topical dosage forms, viscous to semi-solid or solid forms comprising a carrier or one or more excipients compatible with topical application and having a dynamic viscosity preferably greater than water are typically employed. Suitable formulations include, without limitation, solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, and the like, which are, if desired, sterilized or mixed with auxiliary agents (e.g., preservatives, stabilizers, wetting agents, buffers, or salts) for influencing various properties, such as, for example, osmotic pressure. Other suitable topical dosage forms include sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier, is packaged in a mixture with a pressurized volatile (e.g., a gaseous propellant, such as

freon), or in a squeeze bottle. Moisturizers or humectants can also be added to pharmaceutical compositions and dosage forms if desired. Examples of such additional ingredients are well known in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990).

Parenteral Dosage Forms

Parenteral dosage forms can be administered to patients by various routes, including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial. Since administration of parenteral dosage forms typically bypasses the patient's natural defenses against contaminants, parenteral dosage forms are preferably sterile or capable of being sterilized prior to administration to a patient. Examples of parenteral dosage forms include, but are not limited to, solutions ready for injection, dry products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection, suspensions ready for injection, and emulsions.

Suitable vehicles that can be used to provide parenteral dosage forms of the invention are well known to those skilled in the art. Examples include, without limitation: sterile water; Water for Injection USP; saline solution; glucose solution; aqueous vehicles such as but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and propylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate. The solutions are preferably isotonic and have a physiological pH.

Compounds that increase the solubility the active ingredient(s) disclosed herein can also be incorporated into the parenteral dosage forms of the invention.

Transdermal and Mucosal Dosage Forms

Transdermal and mucosal dosage forms of the invention include, but are not limited to, ophthalmic solutions, patches, sprays, aerosols, creams, lotions, suppositories, ointments, gels, solutions, emulsions, suspensions, or other forms

known to one of skill in the art. See, e.g., Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing, Easton, PA (1990); and Introduction to Pharmaceutical Dosage Forms, 4th ed., Lea & Febiger, Philadelphia, PA (1985). Dosage forms suitable for treating mucosal tissues within the oral cavity can be formulated as mouthwashes, as oral gels, or as buccal patches. Further, transdermal dosage forms include "reservoir type" or "matrix type" patches, which can be applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of active ingredient.

Suitable excipients (e.g., carriers and diluents) and other materials that can be used to provide transdermal and mucosal dosage forms encompassed by this invention are well known to those skilled in the pharmaceutical arts, and depend on the particular tissue or organ to which a given pharmaceutical composition or dosage form will be applied. With that fact in mind, typical excipients include, but are not limited to water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and mixtures thereof, to form dosage forms that are non-toxic and pharmaceutically acceptable.

Depending on the specific tissue to be treated, additional components may be used prior to, in conjunction with, or subsequent to treatment with active ingredients of the invention. For example, penetration enhancers can be used to assist in delivering the active ingredients to or across the tissue. Suitable penetration enhancers include, but are not limited to: acetone; various alcohols such as ethanol, oleyl, an tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as TWEEN 80 (polysorbate 80) and SPAN 60 (sorbitan monostearate).

The pH of a pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is applied, may also be adjusted to improve delivery of the active ingredient(s). Similarly, the polarity of a solvent carrier, its ionic strength, or tonicity can be adjusted to improve delivery. Compounds such as stearates can also be added to pharmaceutical compositions or dosage forms to advantageously alter the hydrophilicity or lipophilicity of the active ingredient(s) so as to improve delivery. In this regard, stearates can serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-

enhancing or penetration-enhancing agent. Different hydrates, solvates, polymorphs, or co-crystals of the active ingredient can be used to further adjust the properties of the resulting composition.

In one embodiment of the invention, a pharmaceutical composition comprising a novel olanzapine form is administered orally as needed in an amount of from about 10 mg to about 1000 mg, preferably in an amount of from about 25 mg to about 500 mg, more preferably in an amount from about 40 mg to about 400 mg, and most preferably in an amount of from about 50 mg to about 200 mg. The dosage amounts can be administered in single or divided doses. The dosage amounts and frequencies provided above are encompassed by the terms "therapeutically effective", "prophylactically effective", and "therapeutically or prophylactically effective" as used herein.

The suitability of a particular route of administration employed for a particular active ingredient will depend on the active ingredient itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease or disorder to be treated or prevented.

Preparation of Active Ingredient and Forms Thereof

Olanzapine can be made using various methods known to those skilled in the art. For example, United States Patent No. 5,229,382 discloses illustrative syntheses of olanzapine.

Forms of the invention including salts, co-crystals, or solvates of olanzapine may be prepared by reacting the olanzapine with an appropriate acid, such as an organic or inorganic acid, including without limitation, oxalic acid, succinic acid, malic acid, hydrochloric acid, sulfuric acid, fumaric acid, phosphoric acid, tartaric acid, maleic acid, malonic acid, adipic acid, and benzenesulfonic acid. For example, the process for forming a salt and co-crystal can be carried out in a crystallization solvent in which both reactants (olanzapine free base and acid) are sufficiently soluble.

In one method, in order to achieve crystallization or precipitation, a crystallization solvent is used in which the resulting form, e.g., salt or co-crystal, is only slightly soluble or not soluble. Alternatively, a crystallization solvent is used in which the desired salt and co-crystal is very soluble, and an anti-solvent (or a

crystallization solvent in which the resulting salt is poorly soluble) is added to the solution. Other variants for salt formation or crystallization includes concentrating the salt and co-crystal solution (e.g., by heating, under reduced pressure if necessary, or by slowly evaporating the solvent, for example, at room temperature), or seeding with the addition of seed crystals, or setting up water activity required for hydrate formation.

In certain embodiments, novel soluble forms of olanzapine preferably have a solubility greater than 5 μg/ml, more preferably greater than 10 μg/ml, more preferably greater than 20 μg/ml, more preferably greater than 30 μg/ml, more preferably greater than 40 μg/ml, more preferably greater than 50 μg/ml, and most preferably greater than 100 μg/ml in a solution with a pH of about 1. Preferably, the aqueous solubility is greater than 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 5.0, 10.0, 25.0, or 50.0 mg/mL, for example.

Novel soluble olanzapine forms of the invention include, but are not limited to:

1. an olanzapine fumarate salt that is crystallized in a crystallization solvent comprising approximately equal volumes of methanol and acetone, wherein the olanzapine fumarate salt is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;
2. an olanzapine maleate salt that is crystallized in a crystallization solvent comprising THF, wherein the olanzapine maleate salt is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;
3. an olanzapine malonate salt that is crystallized in a crystallization solvent comprising THF, wherein the olanzapine malonate salt is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;
4. a solvate formed by the recrystallization of olanzapine in a crystallization solvent comprising urea and methanol, wherein the solvate is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;
5. solvates formed by the recrystallization of olanzapine in a crystallization solvent comprising urea and another solvent selected from the group consisting of ethanol, isopropyl alcohol, ethyl acetate, acetone, 1,2-dichloroethane, and THF, wherein the solvates are characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;

6. an olanzapine:nicotinamide co-crystal formed by the recrystallization of olanzapine and nicotinamide in a crystallization solvent comprising 1,2-dichloroethane , wherein the co-crystal is characterized by a powder X-ray diffraction pattern expressed in terms of
2 theta angles;
7. an olanzapine:nicotinamide co-crystal formed by the recrystallization of olanzapine and nicotinamide in a crystallization solvent comprising isopropyl acetate, wherein the co-crystal is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles;
8. an olanzapine:nicotinamide co-crystal formed by the recrystallization of olanzapine and nicotinamide in a crystallization solvent comprising isopropyl acetate, wherein the co-crystal is a quaternary system comprising olanzapine, nicotinamide, water, and isopropyl acetate; and is characterized by a powder X-ray diffraction pattern expressed in terms of 2 theta angles; and
10. olanzapine propylene glycol solvates formed by the recrystallization of olanzapine and propylene glycol in a crystallization solvent comprising isopropyl acetate, wherein the solvates are characterized by powder X-ray diffraction patterns expressed in terms of 2 theta angles.

An olanzapine form of the invention can also be made by reacting olanzapine and a dicarboxylic acid in a heated crystallization solvent to form a reaction product, and thereafter cooling the reaction product to a temperature of between about 0° C to about 10° C over a period of about five to about fifteen hours, or alternatively in a period of less than one hour, to form an olanzapine form that has an aqueous solubility of between about 0.05 mg/ml to about 100 mg/ml.

The invention is described further in the following examples, which are illustrative and in no way limiting.

Materials and Methods

Some or all of the following materials and methods were used in the various experiments described in the examples disclosed herein.

ANALYTICAL EQUIPMENT AND PROCEDURES

THERMOGRAVIMETRIC ANALYSIS

Thermogravimetic analysis of each sample was performed using a Q500 Thermogravimetric Analyzer (TA Instruments, New Castle, DE, U.S.A.), which uses as its control software Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (©2001 TA Instruments-Water LLC), with the following components: QDdv.exe version 1.0.0.78 build 78.2; RHBASE.DLL version 1.0.0.78 build 78.2; RHCOMM.DLL version 1.0.0.78 build 78.0; RHDLL.DLL version 1.0.0.78 build 78.1; an TGA.DLL version 1.0.0.78 build 78.1. In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40 (©1991-2001 TA Instruments-Water LLC).

For all of the experiments, the basic procedure for performing thermogravimetric analysis comprised transferring an aliquot of a sample into a platinum sample pan (Pan part # 952019.906; (TA Instruments, New Castle, DE USA)). The pan was placed on the loading platform and was then automatically loaded into the Q500 Thermogravimetric Analyzer using the control software. Thermograms were obtained by individually heating the sample at 10°C/minute across a temperature range (generally from 25°C to 300°C) under flowing dry nitrogen (compressed nitrogen, grade 4.8 (BOC Gases, Murray Hill, NJ USA)), with a sample purge flow rate of 60 mL/minute and a balance purge flow rate of 40 mL/minute. Thermal transitions (e.g., weight changes) were viewed and analyzed using the analysis software provided with the instrument.

DIFFERENTIAL SCANNING CALORIMETRY

DSC analysis of each sample was performed using a Q1000 Differential Scanning Calorimeter (TA Instruments, New Castle, DE, U.S.A.), which uses Advantage for QW-Series, version 1.0.0.78, Thermal Advantage Release 2.0 (©2001 TA Instruments-Water LLC), with the following components: QDdv.exe version 1.0.0.78 build 78.2; RHBASE.DLL version 1.0.0.78 build 78.2; RHCOMM.DLL version 1.0.0.78 build 78.0; RHDLL.DLL version 1.0.0.78 build 78.1; an TGA.DLL version 1.0.0.78 build 78.1. In addition, the analysis software used was Universal Analysis 2000 for Windows 95/95/2000/NT, version 3.1E; Build 3.1.0.40 (©2001 TA Instruments-Water LLC).

For all of the DSC analyses, an aliquot of a sample was weighed into an aluminum sample pan (Pan part # 900786.091; lid part # 900779.901 (TA Instruments, New Castle DE USA)). The sample pan was sealed either by crimping for dry samples or press fitting for wet samples (such as hydrated or solvated samples). The sample pan was loaded into the Q1000 Differential Sanning Calorimeter, which is equipped with an autosampler, and a thermogram was obtained by individually heating the same using the control software at a rate of 10°C/minute from T_{min} (typically 30°C) to T_{max} (typically 300°C) using an empty aluminum pan as a reference. Dry nitrogen (compressed nitrogen, grade 4.8 (BOC Gases, Murray Hill, NJ USA)) was used as a sample purge gas and was set at a flow rate of 50 mL/minute. Thermal transitions were viewed and analyzed using the analysis software provided with the instrument.

POWDER X-RAY DIFFRACTION

All X-ray powder diffraction patters were obtained using a D/Max Rapid X-ray Diffractometer (Rigaku/MSC, The Woodlands, TX, U.S.A.) equipped with a copper source (Cu/K_α1.5406Å), manual x-y stage, and 0.3 mm collimator. A sample was loaded into a 0.3 mm quartz capillary tube (Charles Supper Company, Natick, MA, U.S.A.) by sectioning off the closed end of the tube and tapping the small, open end of the capillary tube into a bed of the powdered sample or into the sediment of a slurried sample. The precipitate can be amorphous or crystalline. The loaded capillary tube was mounted in a holder that was placed and fitted into the x-y stage. A diffractogram was acquired using control software (RINT Rapid Control Software, Rigaku Rapid/XRD, version 1.0.0 (©1999 Rigaku Co.)) under ambient conditions at a

power setting of 46 kV at 40 mA in transmission mode, while oscillating about the omega-axis from 0-5 degrees at 1 degree/second, and spinning about the phi-axis over 360 degrees at 2 degrees/second. The exposure time was 15 minutes unless otherwise specified.

The diffractogram obtained was integrated of 2-theta from 2-60 degrees and chi (1 segment) from 0-36 degrees at a step size of 0.02 degrees using the *cyllnt* utility in the RINT Rapid display software (RINT Rapid display software, version 1.18 (Rigaku/MSC)) provided by Rigaku with the instrument. The dark counts value was set to 8 as per the system calibration by Rigaku. No normalization or omega, chi or phi offsets were used for the integration.

The relative intensity of peaks in a diffractogram were determined by visual comparison of the peaks in the diffractogram.

SINGLE X-RAY CRYSTALLOGRAPHIC ANALYSIS

Single crystal X-ray crystallographic analyses conducted in connection with the experiments described herein were used to determine unit cell dimensions, space group, and atomic position of all atoms in a compound relative to the origin of its unit cell. The unit cell dimension is defined by three parameters; length of the sides of the cell, relative angles of sides to each other and the volume of the cell. The lengths of the sides of the unit cell are defined by a, b and c. The relative angles of the cell sides are defined by alpha, beta, and gamma. The volume of the cell is defined as V. A more detailed account of unit cells can be found in Chapter 3 of Stout & Jensen, X-Ray Structure Determination; A Practical Guide, Mac Millian Co., New York, N.Y. (1968).

The results of a single crystal X-ray analysis are limited to the crystal placed in the X-ray beam. Crystallographic data on a large group of crystals provides powder X-ray diffraction. If the powder is a pure crystalline compound a simple powder diagram is obtained. To compare the results of a single crystal analysis and powder X-ray analysis a simple calculation can be done converting the single crystal data into a powder X-ray diagram, SHELXTL Plus® computer program, Reference Manual by Siemens Analytical X-ray Instrument, Chapter 10, p. 179-181, 1990. This conversion is possible because the single crystal experiment routinely determines the unit cell dimensions, space group, and atomic positions. These parameters provide a basis to calculate a perfect powder pattern. Comparing this calculated powder pattern and the

powder pattern experimentally obtained from a large collection of crystals will confirm if the results of the two techniques are the same.

Single crystal x-ray data were collected on a Bruker SMART-APEX CCD diffractometer (M. J. Zaworotko, Department of Chemistry, University of South Florida). Lattice parameters were determined from least squares analysis. Reflection data was integrated using the program SAINT. The structure was solved by direct methods and refined by full matrix least squares using the program SHELXTL (Sheldrick, G. M. SHELXTL, Release 5.03; Siemans Analytical X-ray Instruments Inc.: Madison, WI).

The olanzapine forms of the present invention can be characterized, e.g., by the TGA or DSC data or by any one, any two, any three, any four, any five, any six, any seven, any eight, any nine, any ten, or any single integer number of PXRD 2-theta angle peaks, or by single crystal x-ray diffraction data.

EXEMPLIFICATION

Example 1

Olanzapine Fumarate

Fumaric acid (22.1 mg, 0.16 mmol) was added to olanzapine (50 mg, 0.16 mmol). The two solids were dissolved in a 50:50 Methanol: Acetone solution and placed in a freezer at 5 degrees C overnight. The solid material that formed at the bottom of the vial was collected dried and analyzed by PXRD and DSC and determined to be an olanzapine fumarate salt. The olanzapine fumarate salt can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 1 including, but not limited to, 7.39, 9.49, 11.65, 12.71, 13.99, 14.69, 15.83, 17.13, 19.67, 19.99, 21.43, 22.29, and 22.99 degrees 2-theta. The DSC thermogram shows an endothermic transition at about 238 degrees C (Figure 2).

Example 2

Olanzapine Maleate

Equimolar amounts of olanzapine and maleic acid were dissolved in THF and cooled to 5 degrees C. The solid that formed was collected and analyzed by PXRD and DSC and determined to be an olanzapine maleate salt. The olanzapine maleate salt can be characterized by any one, any two, any three, any four, any five, or any six

or more of the peaks in Figure 3 including, but not limited to, 5.57, 9.55, 11.97, 12.95, 16.79, 18.79, 19.25, 21.11, 21.79, 22.23, 22.85, 24.93, 25.77, 26.95, and 28.75 degrees 2-theta. The DSC thermogram shows an endothermic transition at about 196 degrees C (Figure 4).

Example 3

Olanzapine Malonate

Equimolar amounts of olanzapine and malonic acid were dissolved in THF and cooled to 5 degrees C. The solid that formed was collected and analyzed by PXRD and determined to be an olanzapine malonate salt. The olanzapine malonate salt can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 5 including, but not limited to, 7.37, 9.45, 9.85, 12.41, 12.95, 14.83, 16.69, 17.71, 20.51, 21.35, 23.19 and 25.05 degrees 2-theta.

Example 4

Olanzapine Methanol Solvate

This form was obtained from a mixture of olanzapine and urea in methanol. The solution was cooled to 5 degrees C for 2 days and plate like crystals were observed and collected. Samples were analyzed by PXRD, DSC, TGA, and by single crystal x-ray analysis. The olanzapine methanol solvate can be characterized by any one, any two, any three, any four, any five, or any six or more of the peaks in Figure 6 including, but not limited to, 8.61, 9.39, 12.51, 14.19, 16.45, 18.85, 19.97, 20.85, 22.05, 23.09 and 24.73 degrees 2-theta. The DSC thermogram shows two endothermic transitions at about 141 and 196 degrees C (Figure 7). The TGA thermogram shows about a 23 percent weight loss between about 130 and 150 degrees C (Figure 8). Figure 9 shows a packing diagram of the olanzapine methanol solvate.

Crystal data: $C_{18}H_{24}N_4OS$, M = 344.48, monoclinic P2(1)/c; a = 10.1416(8) Å, b = 12.2793(9) Å, c = 14.1147(11) Å, $\alpha = 90°$, $\beta = 91.7860(10)°$, $\gamma = 90°$, T = 373(2) K, Z = 4, $D_c = 1.302$ Mg/m^3, $U = 1756.9(2)$ $Å^3$, $\lambda = 0.71073$ Å. Final residuals were $R_1 = 0.0465$, $wR_2 = 0.1167$ for all data.

Example 5

Preparation of Olanzapine PG solvate

Olanzapine PG solvate was prepared by dissolving 1.05 g of olanzapine in 8 mL of isopropylacetate and 2.0 mL of propylene glycol with heating. The hot liquid was filtered through a 0.2 micrometer nylon syringe filter. Crystallization occurred after cooling to room temperature. The addition of a small amount of seed crystals from a previous reaction followed by sonication for 10 seconds also facilitated crystallization. Olanzapine PG solvate was isolated by suction filtration, rinsed with isopropylacetate and allowed to air dry. The product was a fine yellow powder. The crystals grew in three dimensions, yielding chunks.

A second preparation of olanzapine PG solvate was completed by dissolving 16.2 mg of olanzapine in 0.05 ml of propylene glycol and 0.05 ml of isopropylacetate with heating. The sample was cooled to room temperature and a single crystal from a previous preparation was added. The sample was allowed to sit undisturbed for 2 days during which an aggregate clump of several large crystals grew. The crystals were transferred to filter paper, rinsed with a single drop of isopropylacetate, and dried by dabbing with the filter paper. The rinse procedure was repeated a total of four times with fresh filter paper. Characterization of the product has been achieved via PXRD, DSC, TGA, and Raman spectroscopy.

The PXRD pattern has characteristic peaks as shown for two sample preparations in Figures 10A and 10B. Peaks can be seen at 2-theta angles including but not limited to 8.33, 8.95, 11.75, 14.47, 15.61, 17.95, 19.21, 19.57, 20.65, 21.41, 22.03, and 23.29 in Figure 10A. The crystal can be characterized by any one, any two, any three, any four, any 5, any 6, any 7, any 8, any 9, any 10, any 11, or all 12 of the peaks above or one or a combination of peaks in Figure 10A. In the second representative sample, peaks can be seen at 2-theta angles including, but not limited to, 8.39, 8.89, 13.95, 14.45, 15.55, 17.91, 19.13, 19.55, 20.61, 21.47, 22.07, and 23.31 in Figure 10B. The crystal can be characterized by any one, any two, any three, any four, any 5, any 6, any 7, any 8, any 9, any 10, any 11, or all 12 of the peaks above or one or a combination of peaks in Figure 10B.

Results from DSC show a peak endothermic transition at about 93 degrees C (Figure 11). Results from TGA analysis show an 18.05 % weight loss representing loss of about 1 equivalent of propylene glycol (Figure 12).

Single-crystal x-ray studies of olanzapine PG solvate were also completed. Figure 13 shows a packing diagram of the single-crystal structure of olanzapine PG solvate. The unit cell data are as follows: space group P2(1)/c, A=10.4264(9),

B=13.3916(11), C=14.4424(12), Alpha=90, Beta=95.503(2), Gamma=90, Volume=2007.2(3).

Example 6

Olanzapine:Nicotinamide Co-crystals

Co-crystals of olanzapine and nicotinamide (Forms I, II and III) were prepared. A 9-block experiment was designed with 12 solvents. (A block is a receiving plate, which can be, for example, an industry standard 24 well, 96 well, 384 well, or 1536 well format, or a custom format.) 864 crystallization experiments with 10 co-crystal formers and 3 concentrations were carried out using the CrystalMax™ platform. Form I was obtained from mixtures containing 1:1 and 1:2 molar ratios of olanzapine:nicotinamide in 1,2-dichloroethane. Form II was obtained from mixtures containing a 1:2 molar ratio of olanzapine and nicotinamide in isopropyl acetate. PXRD and DSC characterization of the olanzapine:nicotinamide co-crystals were completed. Fig. 14A shows the PXRD diffractogram of form I after subtraction of background noise. Fig. 14B shows the raw PXRD data of form I. Fig. 15 shows a DSC thermogram of the olanzapine:nicotinamide form I co-crystal. Fig. 16 shows the PXRD diffractogram of olanzapine:nicotinamide form II after subtraction of background noise.

Co-crystals of olanzapine and nicotinamide (Form III) were prepared. Olanzapine (40 microliters of 25 mg/mL stock solution in tetrahydrofuran) and nicotinamide (37.6 microliters of 20 mg/mL stock solution in methanol) were added to a glass vial and dried under a flow of nitrogen. To the solid mixture was added isopropyl acetate (100 microliters) and the vial was sealed with an aluminum cap. The suspension was then heated at 70 degrees C for two hours in order to dissolve all of the solid material. The solution was then cooled to 5 degrees C and maintained at that temperature for 24 hours. After 24 hours the vial was uncapped and the mixture was concentrated to 50 microliters of total volume. The vial was then resealed with an aluminum cap and was maintained at 5 degrees C for an additional 24 hours. Large, yellow plates were observed and were collected (Form III). The solid was characterized with single crystal x-ray diffraction and powder x-ray diffraction. PXRD characterization of the co-crystal was completed. Fig. 17A shows the PXRD diffractogram of form III after subtraction of background noise. Fig. 17B shows the

raw PXRD data of form III. Figs. 18A-D show packing diagrams of the olanzapine:nicotinamide form III co-crystal.

Single crystal x-ray analysis reveals that the olanzapine:nicotinamide (Form III) co-crystal is made up of a ternary system containing olanzapine, nicotinamide, water and isopropyl acetate in the unit cell. The co-crystal crystallizes in the monoclinic space group $P2_1/c$ and contains two olanzapine molecules, one nicotinamide molecule, 4 water molecules and one isopropyl acetate molecule in the asymmetric unit. The packing diagram is made up of a two-dimensional hydrogen-bonded network with the water molecules connecting the olanzapine and nicotinamide moieties. The packing diagram is also comprised of alternating olanzapine and nicotinamide layers connected through hydrogen bonding via the water and isopropyl acetate molecules, as shown in Figure 18B. The olanzapine layer propagates along the b axis at c/4 and 3c/4. The nicotinamide layer propagates along the b axis at c/2. The top of Figure 18C illustrates the nicotinamide superstructure. The nicotinamide molecules form dimers which hydrogen bond to chains of 4 water molecules. The water chains terminate with isopropyl acetate molecules on each side.

Crystal data: $C_{45}H_{64}N_{10}O_7S_2$, M = 921.18, monoclinic P21/c; a = 14.0961(12) Å, b = 12.5984(10) Å, c = 27.219(2) Å, $\alpha = 90°$, $\beta = 97.396(2)°$, $\gamma = 90°$, T = 100(2) K, Z = 4, $D_c = 1.276$ Mg/m^3, U = 4793.6(7) Å^3, $\lambda = 0.71073$ Å; 24952 reflections measured, 8457 unique ($R_{int} = 0.0882$). Final residuals were $R_1 = 0.0676$, $wR_2 = 0.1461$ for $I>2\sigma(I)$, and $R_1 = 0.1187$, $wR_2 = 0.1687$ for all 8457 data.